

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

To:

KATZAROV S.A.
Actn. Jelsch, Emmanuel E.
19, rue des Epinettes
CH-1227 Geneva
SWITZERLAND

(PCT Rule 44.1)

Date of mailing
(day/month/year)

06/10/2004

Applicant's or agent's file reference

14544 - PCT

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/IB2004/001049

International filing date
(day/month/year)

05/04/2004

Applicant

UNIVERSITE DE LAUSANNE

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 18:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 18 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 18 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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Authorized officer

Katarina Faux

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 266).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?**Letter (Section 205(b)):**

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 14544 - PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/IB2004/001049	International filing date (day/month/year) 05/04/2004	(Earliest) Priority Date (day/month/year) 04/04/2003
Applicant UNIVERSITE DE LAUSANNE		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 11 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☒ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box II).

3. ☒ Unity of invention is lacking (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 36.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. 2

☐ as suggested by the applicant.

☒ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

PCT/IB2004/001049

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of Item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
- a. type of material
- ☒ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material
- ☒ in written format
- ☒ in computer readable form
- c. time of filing/furnishing
- ☒ contained in the international application as filed
- ☒ filed together with the international application in computer readable form
- ☐ furnished subsequently to this Authority for the purpose of search
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

Form PCT/ISA/210 (continuation of first sheet (1)) (January 2004)

INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 25-31
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-44 (all partially); 45 (entirely)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)

International Application No. PCT/IB2004/001049

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 25-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

Although claim 31 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound.

International Application No. PCT/IB2004/001049

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-44 (all partially)

A fusion peptabody having features (a), (b), and (c) of claim 1 wherein the EGFR ligand is as defined in claim 10 (a). DNA encoding said peptabody, vector, cells, uses, methods, and kits comprising said peptabody.

2. claims: 1-44 (all partially)

As subject 1 wherein the EGFR ligand is as defined in claim 10 (b).

3. claims: 1-44 (all partially)

As subject 1 wherein the EGFR ligand is as defined in claim 10 (c).

4. claims: As subject 1 1-44 (all partially)

As subject 1 wherein the EGFR ligand is as defined in claim 10 (d).

5. claims: 1-44 (all partially)

As subject 1 wherein the EGFR ligand is as defined in claim 10 (e).

6. claims: 1-44 (all partially)

As subject 1 wherein the EGFR ligand is as defined in claim 10 (f).

7. claims: 1-44 (all partially)

As subject 1 wherein the EGFR ligand is as defined in claim 10 (g).

8. claims: 1-44 (all partially)

As subject 1 wherein the EGFR ligand is as defined in claim 10 (h).

9. claims: 1-44 (all partially)

page 1 of 2

International Application No. PCT/ IB2004/ 001049

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

As subject 1 wherein the EGFR ligand is as defined in claim 10 (i).

10. claims: 1-44 (all partially)

As subject 1 wherein the EGFR ligand is as defined in claim 10 (j).

11. claim: 45

An enhancer sequence as defined in claim 45.

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PC1/182004/001049

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07K19/00 C12N15/62		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07K C12N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, WPI Data, PAJ, EMBASE, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOUIMEL MEHDI ET AL: "Selection of peptides and synthesis of pentameric peptabody molecules reacting specifically with ErbB-2 receptor" INTERNATIONAL JOURNAL OF CANCER, vol. 92, no. 5, 1 June 2001 (2001-06-01), pages 748-755, XP009034136 ISSN: 0020-7136	1,5-7, 11,12, 17-23, 25, 27-30, 35,36,39
Y	the whole document ----- -/--	1-44
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : 'A' document defining the general state of the art which is not considered to be of particular relevance 'E' earlier document but published on or after the international filing date 'L' document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) 'O' document referring to an oral disclosure, use, exhibition or other means 'P' document published prior to the international filing date but later than the priority date claimed 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. 'A' document member of the same patent family		
Date of the actual completion of the international search 17 September 2004		Date of mailing of the international search report 06.10.04
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3018		Authorized officer Valcarcel, R

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Form PCT/ISA/210 (second sheet) (January 2004)

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DEPERTHES DAVID LUC ET AL: "Effect of peptabody anti Epidermal Growth Factor receptors on prostate cancer cell lines proliferation" EUROPEAN UROLOGY SUPPLEMENTS, vol. 1, no. 1, January 2002 (2002-01), page 31, XP009034146 & XVIITH CONGRESS OF THE EUROPEAN ASSOCIATION OF UROLOGY; BIRMINGHAM, ENGLAND, UK; FEBRUARY 23-26, 2002 ISSN: 1569-9056	1-7, 10, 11, 17-23, 25, 27-30, 35, 36, 39
Y	the whole document	1-44
A	----- CAMPBELL I D ET AL: "STRUCTURE-FUNCTION RELATIONSHIPS IN EPIDERMAL GROWTH FACTOR EGF AND TRANSFORMING GROWTH FACTOR-ALPHA TGF-ALPHA" BIOCHEMICAL PHARMACOLOGY, vol. 40, no. 1, 1990, pages 35-40, XP002289670 & FOURTH BIOCHEMICAL PHARMACOLOGY SYMPOSIUM ON NMR METHODS FOR ELUCIDATING MACROMOLECULE-LIGAND INTERA ISSN: 0006-2952 cited in the application the whole document	1-44
A	----- STORTELERS CATELIJNE ET AL: "Epidermal growth factor contains both positive and negative determinants for interaction with ErbB-2/ErbB-3 heterodimers" BIOCHEMISTRY, vol. 41, no. 13, 2 April 2002 (2002-04-02), pages 4292-4301, XP002289671 ISSN: 0006-2960 cited in the application the whole document	1-44
Y	----- LEHTO V-P: "EGF receptor: which way to go?" FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 491, no. 1-2, 23 February 2001 (2001-02-23), pages 1-3, XP004257261 ISSN: 0014-5793 page 2	1-44
	----- -/-	

PCT/IB2004/001049

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ROSE KEITH ET AL: "Polyethyleneglycol-based chains of precise length for chemobodies" PEPTIDES FOR THE NEW MILLENNIUM KLUWER ACADEMIC PUBLISHERS, 3300 AA, DORDRECHT, NETHERLANDS; KLUWER ACADEMIC PUBLISHERS, 101 PHILLIP DRIVE, ASSINIPPI PARK, NORWELL, MA, 02061, USA, 2000, pages 47-49, XP009034147 & 16TH AMERICAN PEPTIDE SYMPOSIUM; MINNEAPOLIS, MI, USA; JUNE 26-JULY 01, 1999 ISSN: 0-7923-6445-7 the whole document	1-44
Y	WO 98/18943 A (CIBA GEIGY AG ; KAJAVA ANDREY (CH); UNIV LAUSANNE (CH); CRAMER RETO () 7 May 1998 (1998-05-07) the whole document	1-44
Y	GARIEPY J ET AL: "Vectorial delivery of macromolecules into cells using peptide-based vehicles" TRENDS IN BIOTECHNOLOGY, ELSEVIER, AMSTERDAM,, GB, vol. 19, no. 1, 1 January 2001 (2001-01-01), pages 21-28, XP004227647 ISSN: 0167-7799 See in particular paragraph bridging pages 23 and 24.	1-44
Y	NOMIZU MOTOYOSHI ET AL: "Multimeric forms of Tyr-Ile-Gly-Ser-Arg (YIGSR) peptide enhance the inhibition of tumor growth and metastasis" CANCER RESEARCH, vol. 53, no. 15, 1993, pages 3459-3461, XP001182805 ISSN: 0008-5472 the whole document	1-44
Y	US 6 350 860 B1 (SABLON ERWIN ET AL) 26 February 2002 (2002-02-26) the whole document	1-44
A	US 6 348 568 B1 (ANWER MOHMED K ET AL) 19 February 2002 (2002-02-19) the whole document	8,45
A	WO 02/066628 A (AVENTIS PHARMA GMBH) 29 August 2002 (2002-08-29) the whole document	8,45
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Form PCT/ISA/210 (continuation of second sheet) (January 2004)

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 571 507 A (BACH JEAN-FRANCOIS ET AL) 5 November 1996 (1996-11-05) the whole document	13-15
A	WO 02/06469 A (COCO WAYNE M ; ENCELL LANCE P (US); ARENSDORF JOSEPH J (US); ENCHIRA B) 24 January 2002 (2002-01-24) SEQ ID NO: 17	1-44
A	CARAGLIA M ET AL: "EGF activates an inducible survival response via the RASfwdarwErk-1/2 pathway to counteract interferon-alpha-mediated apoptosis in epidermoid cancer cells." CELL DEATH AND DIFFERENTIATION, vol. 10, no. 2, February 2003 (2003-02), pages 218-229, XP009034327 ISSN: 1350-9047 the whole document	1-44
Y	MURAYAMA YOICHI: "High concentration of epidermal growth factor induces apoptosis in breast and esophageal cancer cells transplanted into nude mice" ONCOLOGY REPORTS, vol. 1, no. 6, 1994, pages 1055-1062, XP009034329 the whole document	1-44
A	WO 94/18345 A (AFFYMAX TECH NV ; UNIV LELAND STANFORD JUNIOR (US)) 18 August 1994 (1994-08-18) page 49	45
A	GENNITY J ET AL: "SIGNAL PEPTIDE MUTANTS OF ESCHERICHIA COLI" JOURNAL OF BIOENERGETICS AND BIOMEMBRANES, PLENUM PUBLISHING, NEW YORK, NY, US, vol. 22, no. 3, June 1990 (1990-06), pages 233-269, XP009025834 ISSN: 0145-479X the whole document	45

CT/IB2004/001049

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9818943	A	07-05-1998	AU 6909298 A WO 9818943 A1 EP 0938571 A1	22-05-1998 07-05-1998 01-09-1999
US 6350860	B1	26-02-2002	AU 9262598 A CA 2297692 A1 WO 9909055 A2 EP 1015480 A2 US 2003099648 A1	08-03-1999 25-02-1999 25-02-1999 05-07-2000 29-05-2003
US 6348568	B1	19-02-2002	US 6258782 B1 US 6656906 B1 US 2003186874 A1 AU 766995 B2 AU 4194999 A CA 2332338 A1 CN 1310626 T EP 1079846 A1 HR 20000789 A1 HU 0101826 A2 ID 29141 A JP 2002515449 T NO 20005836 A NZ 508352 A PL 344342 A1 TR 200100163 T2 WO 9959615 A1 US 6562787 B1 ZA 200006642 A	10-07-2001 02-12-2003 02-10-2003 30-10-2003 06-12-1999 25-11-1999 29-08-2001 07-03-2001 30-06-2001 28-09-2001 02-08-2001 28-05-2002 19-01-2001 27-02-2004 05-11-2001 21-06-2001 25-11-1999 13-05-2003 28-05-2001
WO 02066628	A	29-08-2002	DE 10108100 A1 BR 0207385 A CA 2438935 A1 WO 02066628 A2 EP 1364030 A2 JP 2004518442 T NO 20033671 A US 2003028001 A1	29-08-2002 10-02-2004 29-08-2002 29-08-2002 26-11-2003 24-06-2004 17-10-2003 06-02-2003
US 5571507	A	05-11-1996	AU 3730093 A CA 2130182 A1 EP 0630383 A1 JP 7507541 T WO 9317038 A1	13-09-1993 02-09-1993 28-12-1994 24-08-1995 02-09-1993
WO 0206469	A	24-01-2002	AU 7355901 A WO 0206469 A2	30-01-2002 24-01-2002
WO 9418345	A	18-08-1994	US 5512435 A AU 6171194 A WO 9418345 A1	30-04-1996 29-08-1994 18-08-1994

Form PCT/ISA/210 (patent family annex) (January 2004)